REMARKS

Claims 9 and 10 have been canceled without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the canceled claims in this or any other patent application. Accordingly, Claims 1-8 and 11-13 are presented for examination.

Correction of Inventorship under 37 CFR §1.48(b)

Applicant requests that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Information Disclosure Statement

The Examiner requested that Applicants provide further information regarding the BLAST results included in the Information Disclosure Statement submitted Sept. 5, 2002. Applicants submit herewith a new Information Disclosure Statement providing the accession numbers and sequences of the sequences identified in the BLAST search.

Applicants inadvertently listed U.S. Patent No. 5,546,637 on the Information Disclosure Statement submitted Sept. 5, 2002 rather than U.S. Patent No. 5,536,637. The Information Disclosure Statement submitted herewith includes U.S. Patent No. 5,536,637.

Priority

The Examiner asserts that the present application is entitled to priority only as of its filing date, May 2, 2002. Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 3, 2002. The preliminary amendment states that the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/380137 filed 8/25/1999, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/12252 filed 6/2/1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/090862 filed 6/26/1998.

Applicants submit that for the reasons stated below, the claimed polypeptides have a credible, substantial, and specific utility. The sequence of SEQ ID NO: 32 was first disclosed in US Provisional Application 60/090862 filed 6/26/1998 in Figure 1. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed polypeptides, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35.

Furthermore, as discussed below, Applicants maintain that the claimed polypeptides have utility for the diagnosis of stomach tumors or lung tumors.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1-13 were rejected as being indefinite because the protein of SEQ ID NO: 32 was not disclosed as being expressed on a cell surface. Accordingly, the Examiner asserts that the claim limitations relating to the "extracellular domain" were indefinite. These limitations have been deleted.

Limitations relating to the "extracellular domain..lacking its associated signal sequences" were also asserted to be indefinite. Applicants maintain that the amendments above render this rejection moot.

Rejections under 35 U.S.C. §101

Claims 1-20 were rejected on the assertion that the claimed subject matter lacks a specific, substantial and credible utility or a well established utility. In particular, the Examiner asserts that the use of the claimed polypeptides to identify molecules that bind to PRO1115 (including agonists and antagonists), diagnostic or therapeutic uses, use as molecular weight markers, use as binding agents, and use for production of antibodies do not satisfy the requirements of 35 U.S.C. §101. The Examiner further asserts that there is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO1115. In addition, while the Examiner acknowledges that the polynucleotides encoding the claimed polypeptides are more highly expressed in normal stomach tissue or normal lung tissue compared to stomach tumors or lung tumors respectively, it is asserted that there is no evidence that the claimed polypeptides are more highly expressed in normal stomach tissue or normal lung tissue compared to stomach tumors or lung tumors respectively. The Examiner asserts that the specification does not teach what is the

normal level of expression, does not indicate how high the expression level is compared to stomach tumor or lung tumor and does not provide a statistical correlation to the level of expression. In addition, the Examiner assets that since the DNA was amplified from the cDNA library from different human tumor and normal tissue samples it is not possible to compare expression levels. The Examiner also asserts that the specification does not describe the specific type of tumor in which the claimed polynucleotides are under-expressed relative to normal tissue and that the expression data has not been corrected for aneuploidy.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility – Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, **the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.** Only after the PTO has made a proper *prima facie* showing of lack of utility does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

Substantial Utility

Applicants have established that the PRO1115 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue and is Useful as a Diagnostic Tool

Example 18 demonstrates that the nucleic acid encoding PRO1115 is expressed at a higher level in normal stomach and normal lung than in stomach tumor and lung tumor respectively. Applicants maintain that this differential expression renders the claimed polypeptide useful in diagnosing cancer and in generating antibodies which may be used as cancer diagnostics.

Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (attached as Exhibit 1). In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application

were made from pooled samples of normal and of tumor tissues. Contrary to the PTO's assertions that this makes the data unreliable, Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal." He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

The PTO also argues that the specification does not provide a utility for the claimed polypeptides because cancerous tissue can be aneuploid, and the data in the instant application were not corrected for aneuploidy, "a higher amplification of a gene does not necessarily mean higher expression or lower in a tissue, but can merely be an indication that the cancer tissue is aneuploid." Office Action at 8. The PTO relies on a single reference, Sen, 2000, Curr. Opin. Oncol. 12:82-88 (hereinafter Sen).

Applicants agree that Sen teaches that most cancerous tissues are aneuploid, and that it is possible that the results reported in Example 18 may be due to aneuploidy in the tumor cells

tested. However, Applicants fail to see how it is relevant to the utility of the claimed polypeptides, whether the differential expression reported in Example 18 is due to aneuploidy or not. Regardless of whether the differential expression of the gene encoding PRO1115 is a result of increased or decreased transcription of the gene, aneuploidy, or some other regulatory mechanism, the fact remains that it is more highly expressed in normal stomach tissue or normal lung tissue relative to stomach tumor or lung tumor respectively, and it is therefore useful as a diagnostic tool for cancer since it can be used as a molecular marker for cancer.

Applicants have established that the Accepted Understanding in the Art is that there is a Direct Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

The PTO argues that there is no supporting evidence that the claimed polypeptides are more highly expressed in normal stomach tissue or normal lung tissue compared to stomach tumor or lung tumor respectively. The PTO also states that the literature reports that it does not *necessarily* follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression. Relying on Pennica *et al.*, 1998, PNAS USA 95:14717-14722 (hereinafter Pennica), the PTO states that one cannot extrapolate the expression data provided in the specification to support the implicit assertion that PRO1115 can be used in cancer diagnosis or therapy.

Applicants respectfully submit that the PTO is confusing the relationship between an increase in copy number of a gene or gene amplification on the one hand, and increased expression of a gene or mRNA expression on the other. The PTO focuses on the statement from Pennica that the *WISP-2* gene DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient. Office Action at 8. As an aside, it should be noted that this result may not even be real, as the authors explain: "Because the center of the 20q13 amplicon [of which *WISP-2* is a part] has not yet been identified, it is possible that the apparent amplification observed for *WISP-2* may be caused by another gene in this amplicon." Pennica at 14722 (emphasis added).

However, even if the lack of correlation between DNA copy number and mRNA level in Pennica is real, Pennica says nothing about a lack of correlation between the level of mRNA and the level of protein expression – Pennica did not even look at protein expression. It is the

correlation between mRNA level, as assessed by probing the cDNA library, and the level of protein expression which is at issue here, not the correlation of gene copy number and mRNA levels. The data Applicants report in Example 18 indicate that there are fewer copies of the mRNA encoding PRO115 in stomach tumors or lung tumors than normal stomach tissue or normal lung tissue respectively. Nothing in Pennica is contrary to Applicants' assertion that it is well-established in the art that the level of protein is positively correlated to the level of mRNA.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. Even if Pennica supported the PTO's argument, which it does not, one contrary example does not establish that one of skill in the art would find it is more likely than not, that in general, there is no correlation between mRNA level and protein levels. In fact, the working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels.

Applicants submit herewith as Exhibit 2 a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 3), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in

> abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

Together, the declarations of Mr. Grimaldi and Dr. Polakis establish that the accepted understanding in the art is that there is a direct correlation between the level of mRNA and the level of the encoded protein. In light of the lack of support for any argument by the PTO to the contrary, Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that because the PRO1115 mRNA is expressed at a lower level in stomach tumors and lung tumors than normal stomach tissue or normal lung tissue respectively, the PRO1115 polypeptide will also be expressed at a lower level in stomach tumors and lung tumors than normal stomach tissue or normal lung tissue respectively. One of skill in the art would recognize that a protein which is differentially expressed in certain cancer cells compared to the corresponding normal tissue would have utility as a diagnostic tool. As the PTO has acknowledged, "if the protein has utility, then this confers utility upon the polynucleotide...." Thus, Applicants submit that they have established that it is more likely than not that one of skill in the art would recognize the asserted utility of the PRO1115 polypeptide, and the nucleic acids which encode it, as a cancer diagnostic tool.

The use of the PRO polypeptides to generate antibodies is disclosed in the specification at Paragraph [0361]-Paragraph [0396] and Paragraph [0493]-Paragraph [0499]. The use of antibodies against the PRO polypeptides as diagnostic tools is disclosed in the specification in Paragraph [0407].

The utility guidelines recognize that the diagnosis of cancer is a credible utility. (See page 5 of the Revised Interim Utility Guidelines Training Materials which provide that use as a diagnostic marker is a credible utility.)

Furthermore, the utility of the claimed polypeptides as a stomach tumor or lung tumor diagnostic is specific to the claimed polypeptides and is not a characteristic of polypeptides in general.

Finally, stomach tumor or lung tumor diagnosis is a substantial utility. (See the caveat in Example 12 of the Revised Interim Utility Guidelines Training Materials, pages 69-70, which states that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin cells and antibodies against the protein can be used to diagnosis cancer.)

Together, the declarations of Mr. Grimaldi and Dr. Polakis establish that the accepted understanding in the art is that there is a direct correlation between the level of mRNA and the level of the encoded protein. In light of the lack of support for any argument by the PTO to the contrary, Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that because the PRO1115 mRNA is expressed at a higher level in normal stomach tissue or normal lung tissue than stomach tumor or lung tumor respectively, the PRO1115 polypeptide will also be expressed at a higher level in normal stomach tissue or normal lung tissue than stomach tumor or lung tumor respectively. One of skill in the art would recognize that a protein which is differentially expressed in certain cancer cells compared to the corresponding normal tissue would have utility as a diagnostic tool. Thus, Applicants submit that they have established that it is more likely than not that one of skill in the art would recognize the asserted utility of the claimed polypeptides as a cancer diagnostic tool.

The Claimed Polypeptide would have Diagnostic Utility even if there is no Positive Correlation between Gene Expression and Expression of the Encoded Polypeptide

Even assuming *arguendo* that, there is no direct correlation between gene expression and protein expression for PRO1115, which Applicants submit is not true, a polypeptide encoded by a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the Grimaldi Declaration, Exhibit 2, Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene

expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 4), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin, submitted herewith (attached as Exhibit 5). The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, a polypeptide encoded by a gene that is differentially expressed in cancer would still have utility. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed polypeptides.

Conclusion

The PTO has asserted two arguments for why there is a lack of a substantial utility: (1) that the data reporting differential expression of the PRO1115 gene in certain cancers is not reliable; and, (2) that because there is no necessary correlation between gene amplification and protein expression, the claimed polypeptides cannot be used as cancer diagnostic or therapeutic tools. Applicants have addressed each of these arguments in turn.

First, the Applicants provide a declaration stating that the data in Example 18 reporting higher expression of the PRO1115 gene in normal stomach tissue or normal lung tissue relative to stomach tumor or lung tumor are real and significant. This declaration also indicates that

given the relative difference in expression levels, the claimed polypeptides have utility as cancer diagnostic tools. Applicants have also shown that whether the differential expression of the PRO1115 polypeptide is due to aneuploidy or not does not affect its usefulness as a diagnostic tool.

Next, the Applicants have shown that the reference cited by the PTO to support its conclusion that there is no necessary correlation between the level of gene expression and mRNA or protein expression does not support the PTO's position. Applicants have presented the declarations of two experts in the field along with supporting references which establish that the general, accepted view of those of skill in the art is that there is a direct correlation between mRNA levels and the encoded protein levels. Thus, one of skill in the art would find that it is more likely than not that the claimed polypeptide has utility as a diagnostic tool for cancer.

Applicants have also presented the declarations of two experts in the field, along with supporting references, which establish that even in the anomalous case where there is no positive correlation between gene expression and expression of the encoded protein, the simultaneous monitoring of both is useful for diagnosis and further classification of the cancer.

Finally, the PTO asserts that there is no asserted specific utility because there is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature associated with PRO1115. Applicants have pointed out that the substantial utilities described above are specific to the claimed polypeptides because PRO1115 is differentially expressed in certain cancer tissue compared to the corresponding normal tissue. This is not a general utility that would apply to the broad class of polypeptides.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed polypeptides as a diagnostic agent. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed polypeptides set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection Under 35 U.S.C. §112, first paragraph

Claims 1-13 were rejected under 35 U.S.C. §112, first paragraph on the assertion that because the claimed polypeptides lack utility one skilled in the art would not know how to use them. Applicants maintain that the claimed polypeptides have utility for the reasons stated above.

Claims 1-5, 12 and 13 were rejected under 35 U.S.C. §112, first paragraph on the assertion that they contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed.

The Examiner asserts that in order to claim a genus the specification must provide sufficient distinguishing characteristics of the genus, such as complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product or any combination thereof. The Examiner asserts that the specification does not contain sufficient description to support claims to polynucleotides having at least 80%, 85%, 95% or 99% sequence identity to the claimed sequence. Applicant notes that the claims in the present application are drawn to polypeptides rather than polynucleotides but assumes that the Examiner intended to refer to polypeptides.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); see also *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. The instant invention, defined by the amended claims, concerns polypeptides having a specified sequence identity with the disclosed polypeptide sequence of SEQ ID NO: 32, and which as amended herein, are "expressed at a higher level in normal stomach and normal lung than in stomach tumor and lung tumor respectively, or are encoded by a polynucleotide that is expressed at a higher level in normal stomach and normal lung than in stomach tumor and lung tumor respectively". Based on the detailed description of the cloning and expression of variants of PRO1115 in the specification, the description of the gene amplification assay, the actual reduction to practice of sequences SEQ ID NOs: 31 and 32, and the functional recitation in the instant claims, Applicants submit that one of skill in the art would know that Applicants possessed the invention as claimed in the instant claims. Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejection under 35 U.S.C. §102 – Anticipation

Claims 1-5 were rejected under 35 U.S.C. §102(e) as being anticipated by Collier,Accession No. Q9BWY7, June 2001. Applicants note that because Collier is not a U.S. patent application it cannot be prior art under 35 U.S.C. §102(e). Furthermore, Applicants submit that because Collier was published in 2001 it does not constitute prior art to the present application under any subsection of 35 U.S.C. §102. In particular, as discussed above, the sequence of SEQ ID NO: 32 was first disclosed in US Provisional Application 60/090862 filed

6/26/1998. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed polypeptides, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. Thus, Applicants are entitled to a priority date of at least **August 24, 2000**. Because Collier was published after the priority date of the present application, they are not available as prior art against the present application.

Rejection under 35 U.S.C. §103

Claims 12 and 13 were rejected under 35 U.S.C. §103 as being obvious over Collier ,Accession No. Q9BWY7, June 2001 in view of Turner et al. Accession No. AAX146414 (WO 0134804A1, published May 2001). As discussed above, Collier is not prior art to the present application. Applicants also submit that Turner et al. is also not prior art to the present application because Turner was published in May 2001 and, as discussed above, the present application is entitled to priority prior to that date.

Accordingly, Applicants request that the PTO reconsider and withdraw the rejection under 35 U.S.C. §103.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Sept. 16, 2004

By: 

Daniel Hart
Registration No. 40,637
Attorney of Record
Customer No. 30,313
(619) 235-8550

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